Infectious Diseases Society of America

PEDIATRIC INFECTIOUS DISEASES SOCIETY

Antibiotic Development for Patients with Serious Infections and Unmet Need

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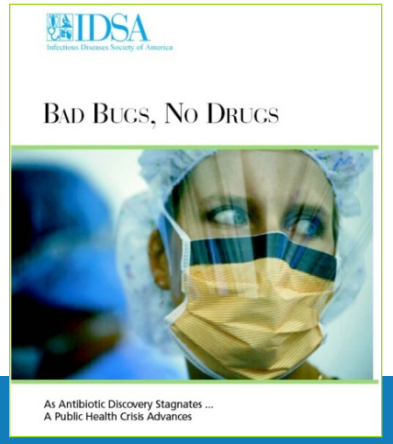
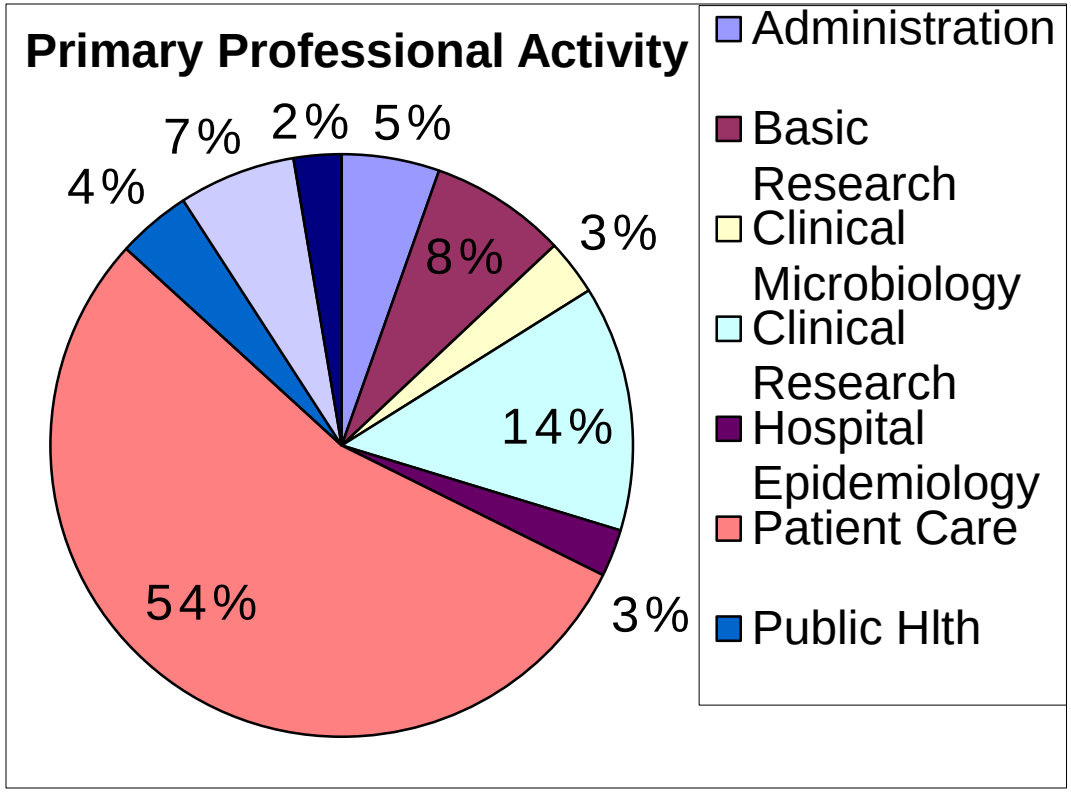
December 4, 2014



IDSA Membership

10,000+ strong
Majority physicians providing clinical care, contributing to clinical care



Physician Perspective:
The Tragedy of *Ineffective* Antibiotics - The Crisis is Now

Premature Death

Rebecca Lohsen
(17 yr)--Dead

Carlos Don
(12 yr)--Dead

Ricky Lannetti
(21 yr)--Dead

Life-altering Disability

Tom Dukes: colostomy, lost 8” colon

Addie Rereich, 11yo
Double lung transplant
Stroke, nearly blind
$6 million hospital bill

Unmet Need

- Any antimicrobials to treat Gram-negative infections
- Better antimicrobials to treat Gram-positive infections
- Oral antibiotics for cUTIs, STIs (gonorrhea), respiratory infections, step-down therapy
- Robust and sustainable pipeline of anti-infective drugs to provide for our patients now and in future generations

John Bartlett, IDWeek 2013

Antibiotic Resistance: Realities for Patients and Physicians

- The only antibiotic remaining to treat many Gram negative bacterial infections is Colistin.
- Colistin is toxic; it's use causes kidney failure.
- Colistin had not been used in 30 years, but has been pulled off the shelves because there is nothing else.
- Gram negative bacteria are now developing resistance even to Colistin.
- Soon there will be no alternatives for these patients.

Current alternatives for these patients: "Do you want to die, or to be on dialysis for the rest of your life or until you can get a kidney transplant?"

Off Label Use: What do we do when information we need is not in label?

Facing severe infections caused by MDROs and dwindling antibiotic arsenal, off label use is often necessary.

- Library
- Assemble available information
  - Animal studies
  - Case reports
  - Small series
- If label contains good information, greater likelihood of my making best decision based on available data
  - Older labels contain large tables of PK data at important sites (e.g., brain, bone) that is very useful clinically

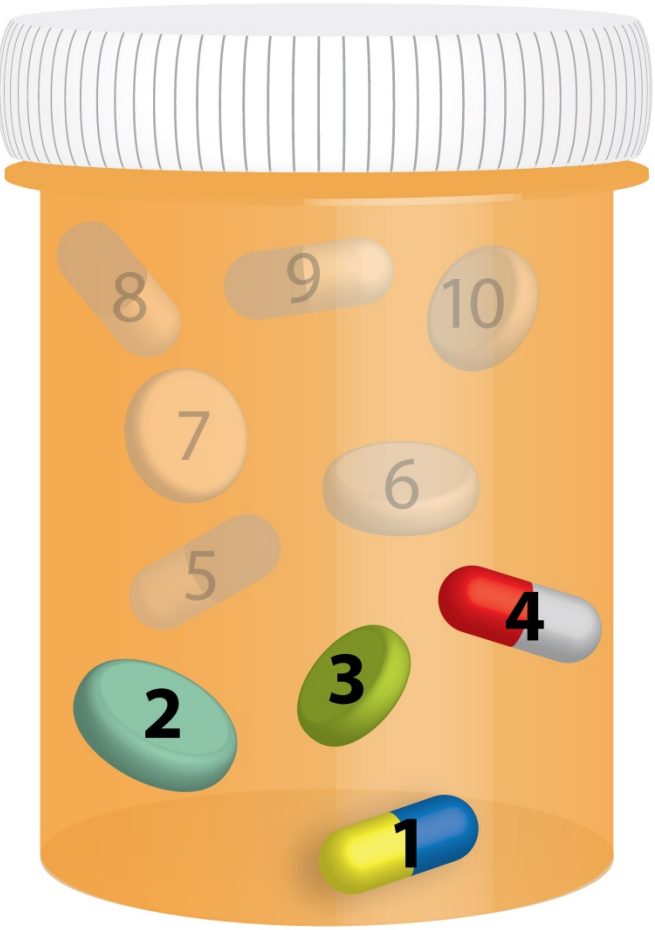
Adapted from Boucher, The Development of New Antibacterial Products: Charting a Course for the Future, July, 2014

Off Label Use: What do we do when information we need is not in label?

- Many therapies we rely upon in Infectious Diseases are based on Tier B or C, even Tier D, type data
  - —Infectious diseases are caused by pathogens with measurable MICs
    - Not necessary to include resistant pathogens in studies in order to learn about the potential benefit or safety profile of a drug in treating them
  - —PK is predictive

Boucher, The Development of New Antibacterial Products: Charting a Course for the Future, July, 2014

Status of IDSA 10 x ‘20 Initiative: Some Progress, More Needed



Bad Bugs Need Drugs

10x'20

Ten new **ANTIBIOTICS** by 2020

10
9
8
7
6
5

4 oritavancin
The Medicines Company; Approved: August 6, 2014

3 tedizolid phosphate
Cubist Pharmaceuticals, Inc.; Approved: June 20, 2014

2 dalbavancin
Durata Therapeutics; Approved: May 23, 2014

1 ceftaroline fosamil
Forest Laboratories, Inc.; Approved: October 29, 2010

Stimulating Development of Antibiotics for Unmet Needs

- **Economic Incentives** (push and pull): Building on GAIN Act
  - Tax Credits
  - Funding for key federal agencies, including NIAID, BARDA
  - Improved Reimbursement
- **Feasible Regulatory Pathways**
  - Companies cannot populate traditional, large-scale clinical trials for new drugs to treat infections that currently occur in small number of patients
  - Many barriers to patient enrollment in clinical trials: small patient population, lack of diagnostics, severely ill patients, prior antibiotic use
  - Superiority trials are typically impossible

Impossibility of Superiority Trials

Superiority clinical trials are often not appropriate or feasible for the study of new antibiotics.

- Placebo unethical for serious infections
- For some infections caused by highly resistant pathogens, there may be no appropriate comparator
- Unethical to use an antibiotic to which bacteria are resistant as a comparator

Regulatory solution: Antibiotic Development to Advance Patient Treatment (ADAPT) Act

- Establishes a **limited population antibacterial drug (LPAD) approval pathway** to address serious or life-threatening infections where an unmet medical need exists
- ADAPT/LPAD drugs would be approved based upon **smaller, faster, and less expensive clinical trials**; drugs must still be demonstrated to be safe and effective for indicated population based upon current FDA evidentiary standards
- ADAPT/LPAD drugs' **labeling** must make clear to the healthcare community that these drugs are approved for a limited population and must be used appropriately
- ADAPT/LPAD drugs' use would be **monitored** by CDC's National Healthcare Safety Network (NHSN)

President's Council of Advisors on Science and Technology (PCAST)

September 2014 PCAST Report on Antibiotic Resistance recommends developing new regulatory pathways to evaluate urgently needed antibiotics.

"FDA should use existing mechanisms to facilitate approval of drugs based on demonstration of safety and efficacy in specific patients infected with antibiotic-resistant bacteria, while discouraging use in other patient populations. In parallel, the Administration should support the passage of legislation that explicitly authorizes the FDA to establish a full Special Medical Use pathway for antibiotics."

Data Packages Smaller but Valuable Given Unmet Need

In the label we hope to see:

- In vitro and in vivo data
  - —Activity of new drug vs. resistant pathogens
- Pharmacology, drug interaction data
- PK data
  - —Drug levels in relevant tissues/sites of infection
- Everything re: prior human experience (even single cases)
  - —A few well described patients with infection(s) of interest more useful than PK/PD alone

Boucher, The Development of New Antibacterial Products: Charting a Course for the Future, July, 2014

Data Packages Smaller but Valuable Given Unmet Need

In the label:

- Clinical studies
  - Optimal to include patients from the United States
  - —Small randomized trial in multiple body sites may be useful
  - —Historical controls useful
  - —Studies of less severely ill patients also useful
    - —Skin infections, UTI, etc.
- Safety data

Boucher, The Development of New Antibacterial Products: Charting a Course for the Future, July, 2014

How will clinicians interpret data on labels of LPAD drugs? Risk/Benefit

- Clinicians understand how to interpret data from adequate and well controlled trials versus observational data, case reports, etc.
- Small # responses/recovery in severe disease (especially those with low chance of spontaneous response), shows efficacy
  - Patients across sites
  - Few pneumonia, brain, abdominal infections
  - Anything with bloodstream infection
- Patients at risk
  - when we are forced to use toxic drugs like colistin with little to no guiding information
  - When they develop syndromes that have not yet been studied

Boucher, The Development of New Antibacterial Products: Charting a Course for the Future, July, 2014

IDSA's Goal: Ensure Antibiotic Availability

Prior generations gave us the gift of antibiotics. Today, we have a moral obligation to ensure this global treasure is available for our children and future generations.

We must appropriately balance the risk of allowing smaller, more feasible clinical trials against the far greater risk of prohibiting the development of urgently needed new antibiotics and entering the post-antibiotic era.

IDSA

10x'20

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